REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1, 3-4, 11-28, 41, and 62-71, the only claims pending and under examination.

Claims 1, 3-4, 11-28, 41, and 62-68 have been examined and rejected.

Claims 2, 5-10, 53-56, and 58-61 have been cancelled.

Claims 29-40, 42-52, and 57 have been withdrawn.

Claims 1 and 65 have been amended. Support for these amendments can be found in the specification, for example on p. 5, lines 14-26, and p. 56, line 25 to p. 57, line 9. Claims 69-71 have been added. Support for new Claim 69 can be found in the specification, for example, on p. p. 56, line 25-28. Support for new Claim 70 can be found in the specification, for example, on p. 48, line 24 to p. 49, line 5, and p. 76, lines 16-20. Support for new Claim 71 can be found in the specification, for example, on p. 48, line 24 to p. 49, line 21. Accordingly, no new matter has been added. As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Claim Rejections - 35 U.S.C. § 102

The Applicants thank the Examiner for the withdrawal of the rejection of Claims 1, 3, 4, 14, 19-22, 28, 41, and 62 under 35 U.S.C. § 102(b) over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297).

The Applicants thank the Examiner for the withdrawal of the rejection of Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, and 62 under 35 U.S.C. § 102(b) over Brevetti et al. (Brief communications, Nov. 1981, p 938-941).

The Applicants thank the Examiner for the withdrawal of the rejection of Claims 1, 21, 23-25, and 28 under 35 U.S.C. § 102(b) over Davies, et al. (The J of Intl Med Research, 1988, 16, 173-181).

The Applicants thank the Examiner for the withdrawal of the rejection of Claims 1 and 20 under 35 U.S.C. § 102(b) over Broder, et al. (U.S. Patent 6,284,800).

Claim Rejection - 35 U.S.C. § 112

Claims 1, 3, 4, 11-28, 41, 62-68 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 U.S.P.Q.2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991).

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, paragraph 1 "Written Description" Requirement (Federal Register 66, No. 4, January 5, 2001; hereinafter the “Written Description Guidelines”) provides instructions for examining patent applications for compliance with the written description requirement of 35 U.S.C.§112, first paragraph.

The Written Description Guidelines state:

(1) There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed;

(2) The Examiner has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims;

(3) Consequently, rejection of an original claim for lack of written description should be rare;

(4) An Examiner should review the entire application to understand how Applicant provides support for the claimed invention; and

(5) Such a review is conducted from a standpoint of one of skill in the art at the time the application was filed and should include a determination of the field of the invention and the level of skill and knowledge in the art.

In making the rejection, the Office continues to allege that the specification does not provide adequate support for the claimed invention because specific examples are not provided. However, the Applicants contend that the inventors of the subject invention have discovered that autonomic nervous system disturbances are the underlying cause of a wide range of diseases that appear to be a heterogeneous, unrelated group of conditions. The inventors of the subject invention have therefore formulated novel pharmacologic strategies to treat various disease conditions *by modulating autonomic function as the basis of therapy*. The Applicants therefore contend that specific examples and doses are not necessary to provide an adequate written description of this novel approach of modulating autonomic function to treat multiple diseases, as the Office suggests.

The Applicants further contend that the drugs in question (e.g., beta blockers, and non-steroidal anti-inflammatory drugs (NSAIDs)) are well-known agents, with well-known side-effects, which are used in well-known dosages. In particular, the elected species propranolol is a well-known drug, which is being used in a standard dosage. The Applicants maintain that one of skill in the art would recognize that the specification when viewed in the context of the knowledge of those of ordinary skill in the art provides sufficient written description support for the claims. The Applicants maintain that there is adequate support in the specification for the rejected claims directed to novel treatment methods for treating a condition caused by an autonomic nervous system abnormality, by using well-known drugs that are known to affect the autonomic nervous system. As such,

the written description is sufficient to conclude that the inventors had possession of the claimed invention.

The Office continues to allege that the specification does not "provide data or show examples of actual administration of beta blockers in conditions arising from modulation of autonomic nervous system"; that "there is no specific data or examples providing administration of a non-beta blocker along with a beta blocker"; and that the specification does not give any specific guidance to age associated conditions resulting from modulation of autonomic nervous system regarding criteria for the dosages, the counter indications, dosage regimens, criteria if patients suffer from multiple associated conditions (Final Office Action, pp. 35-36).

In making the rejection, the Office has alleged that specific guidance on dosages and contra-indications is required (Office Action, p. 36) and cites conflicting or incomplete information from Wikipedia on the uses and side-effects of beta-blockers and NSAIDS. For example, the Office states "[t]he Wikipedia document on propranolol indicates that beta blockers are downgraded to fourth line drugs for treating hypertension as they perform less well than other drugs..." (Final Office Action, p. 36). However, the Applicants point out that hypertension is also listed first on the Wikipedia site under indications for use and dosage regimens. The Office also allegedly provides evidence that dosages used with propranolol are unclear, citing "e.g., hypertension (120-130 mg), tachyarrhythmia (10-40 mg)". However, the Applicants point out that a closer reading of the Wikipedia website reveals that the dosages listed are: hypertension 120-320 mg *daily*, and tachyarrhythmia 10mg- 40mg *3-4 times daily*. In fact, these doses are identical. For example, a dose for hypertension may be 120mg per day, and a dose for tachyarrhythmia may also be 120 mg per day (i.e., 40 mg x 3; or 30 mg x 4), etc. Therefore, the Applicants maintain that contrary to the Office's assertions, standard dosages of the elected species propranolol are clear, and are consistent with the dosages cited in the specification.

The Office also concludes that "precautions need to be taken in administering an NSAID along with a beta blocker for patients with cardiovascular indications" (Final Office Action, p. 37), citing Wikipedia. The Wikipedia site actually states "If this link is found to be causal, NSAIDs are estimated to be responsible for up to 20 percent of hospital admissions [in patients with a history of cardiac disease] for congestive heart failure." There is actually no mention of administering an NSAID with a beta blocker in the cited portion of the reference.

As discussed in the previous response, the specification does provide adequate description for methods of administering beta-blockers to treat a subject, for example, on p. 14, line 14 to p. 25, line 4. Disclosure of conditions that may be treated using the subject methods can be found, for example, on p. 56, lines 3-11, and p. 57, lines 10 to p. 59, line 11. Extensive support for the theory of novel pharmacologic strategies to treat various disease conditions by modulating autonomic function as the basis of therapy including multiple specific examples of diseases that can be treated along with references can be found on p. 4, line 9 to p. 5, line 26, and p. 59, line 11 to p. 67, line 29. There are specific examples disclosed in the specification, for example, as in the treatment of sudden infant death syndrome (SIDS), or conditions associated with aging. In the example of SIDS, (as disclosed on p. 59, lines 19-25, and p. 60, line 20 to p. 61, line 12) the inventors have discovered that a maladaptive shift to sympathetic bias may be a key determinant of SIDS, and cite multiple references in support of this assertion. In the example of aging-associated conditions (as disclosed on p. 65, line 20 to p. 67, line 12), the inventors have determined that many conditions of aging are manifestations of sympathetic bias unmasked by withdrawal of parasympathetic function. Additional citations in support of this assertion can be found on p. 66, lines 13-27.

In summary, it appears to the Applicants that the Office is alleging that beta-blockers and NSAIDS have side effects, interactions with other drugs, dosages

that can vary depending on the patient or the condition treated, and that patients need to be monitored. The Applicants contend that these are standard issues for any medical treatment, and are routinely dealt with by physicians. Furthermore, the rejected claims are directed to *novel treatment methods for treating a condition by modulating autonomic function as the basis of therapy, by using well-known drugs that are known to affect the autonomic nervous system*. The inventors of the subject invention have discovered that autonomic nervous system disturbances are the underlying cause of a wide range of diseases that appear to be a heterogeneous, unrelated group of conditions. The Office has failed to provide evidence or reasons why a person skilled in the art would *not* recognize that the written description of the invention, as would be understood by one of skill in the art, i.e., administration and dosage for beta blockers and NSAIDs, provides support for the claims.

Therefore, the Applicants maintain that there is adequate written description in the specification in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. The Examiner has not established with sufficient evidence why a person skilled in the art would not recognize that the written description of the invention provides support for the claims, and therefore, the Applicants respectfully request that the rejection of Claims 1, 3, 4, 11-28, 41, 62-68 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1, 3, 4, 11-28, 41, 62-68 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled by the specification.

In making the rejection, the Office again alleges that the specification does not provide sufficient guidance for the current claims. The Examiner alleges that the specification does not reasonably provide enablement for treating all the disorders listed in Claim 1, with the non-beta blocking agents listed in Claim 24.

The Office further alleges that it would require "undue, unpredictable experimentation to practice the claimed invention" (Final Office Action, p. 41)

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation."[1]

Under *In re Wands*, a determination of enablement requires consideration of eight factors, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.[2] Accordingly, under *In re Wands*, a determination of enablement is based on the combination of the factors, taken as a whole, not based solely on a single factor.

The Applicants contend that inventors of the subject invention have discovered that autonomic nervous system disturbances are the underlying cause of a wide range of disease conditions that appear to be a complex, heterogeneous, unrelated group. The present invention involves methods of treating conditions *that are caused by an autonomic nervous system abnormality*. In other words, the conditions all contain the common element of being caused by an autonomic nervous system abnormality, and therefore, are not as broad as the Examiner suggests.

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1. *United States v. Telectronics, Inc.,* 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied,* 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

2. *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The inventive step, therefore, is a method of treating a subject for a condition caused by a previously undiscovered underlying cause, with a well-known agent (e.g., a beta-blocker), which for some of the conditions is a non-traditional agent, because the inventors have discovered that modulation of the autonomic nervous system can result in effective treatment for the condition. There is not, as the Examiner alleges, a requirement for testing each beta-blocker for all conditions listed, with every single non-beta blocker listed.

The inventors of the subject invention have therefore formulated novel pharmacologic strategies to treat conditions including disease conditions by modulating autonomic function as the basis of therapy. Extensive support for this theory including multiple specific examples of diseases that can be treated along with references can be found in the specification, for example on p. 4, line 9 to p. 5, line 26, and p. 59, line 11 to p. 67, line 29. Disclosure of conditions that may be treated using the subject methods can be found on p. 56, lines 3-11, and p. 57, line 10 to p. 59, line 11. There are specific examples disclosed in the specification, for example, as in the example of treatment of sudden infant death syndrome (SIDS), as disclosed on p. 59, lines 19-25, and p. 60, line 20 to p. 61, line 12. In this disclosure, the inventors have disclosed that a maladaptive shift to sympathetic bias may be a key determinant of SIDS, and additionally cited multiple references in support of this assertion. In the example of aging-associated conditions (as disclosed on p. 65, line 20 to p. 67, line 12), the inventors have determined that many conditions of aging are manifestations of sympathetic bias unmasked by withdrawal of parasympathetic function. Additional citations in support of the assertion can be found on p. 66, lines 13-27.

Treatment is with agents that are well-known in the art, i.e., beta-blockers. Directions for treatment of the identified conditions by administering beta-blockers can be found, for example, on p. 14, line 14 to p. 25, line 4. Furthermore, the specification discloses methods of treating a condition such that the activities of the

parasympathetic and sympathetic systems are modulated, for example, on p. 10, lines 11-27. Additionally, the specification discloses methods of determining the parasympathetic and sympathetic functions, for example, on p. 48, lines 24-29.

The arguments previously presented by the Applicants re: *In Re Wands*, as well as a discussion of the references provided by the Office still apply with the same force, however they will not be repeated in their entirety here. For the reasons set forth above as well as in the previous responses, the Applicants maintain that the enablement requirement to practice the method of treatment has been met because 1) the amount of experimentation required to practice the claimed methods would not be undue and excessive 2) guidance is given on how to practice such methods of treatment 3) it is not necessary to provide a working example, 4) the relative skill of those in the art is high, and 5) the breadth of claims is enabled by the specification. As such, one skilled in the art would be able to perform the experiments as a matter of routine. The specification, therefore, provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

Accordingly, the Applicants maintain that the current claims directed to methods of treating a subject for a condition caused by an autonomic nervous system abnormality comprising providing a subject known to suffer from an autonomic nervous system abnormality, and administering to the subject an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject to treat the subject are sufficiently enabled by the specification.

In view of the foregoing discussion, the Applicants submit that the current claims are adequately enabled by the specification. Accordingly, the Applicants

respectfully request that the rejection of Claims 1, 3, 4, 11-28, 41, 62-68 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1 and 63 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003) in view of Rang et al. (Rang, et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann, et al. (US 2004/0147969).

An element of the rejected claims as currently amended is providing a subject known to suffer from an autonomic nervous system abnormality, and administering to the subject an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject to treat the subject.

In making the rejection, the Office cited Lampert for teaching that propranolol therapy improves recovery of parasympathetic tone after acute myocardial infarction. However, Lampert does not teach the element of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering to the subject an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, as in the amended claims.

Lampert also does not suggest this element, because the study was designed to "elucidate the mechanisms by which ß blockers decrease mortality after acute myocardial infarction". There is therefore no suggestion of providing a

subject known to suffer from an autonomic nervous system abnormality. There is also no suggestion of producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

The Office also cites Rang for teaching non-invasive procedures for assessing autonomic cardiovascular control in patients with hypertensive disorder, and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. The Applicants note that the Autonomic Dysfunction document provided is from Oulu University, not Duke University as stated in the Office Action. Also, Mann was cited for teaching a control feedback loop, however a control feedback loop is not an element of these rejected claims.

The Office concludes that it would have been obvious to have determined equality in parasympathetic and sympathetic functions using the methods of Rang and the ADD, because "one having ordinary skill in the art would have been motivated to determine the sympathetic and parasympathetic functions are substantially equal" because "assessment of autonomic dysfunction would help in regulating the body functions such as heart rate, blood pressure, temperature regulation, etc." (Final Office Action, p. 12-13)

However, the Applicants contend that neither Rang nor the Autonomic Dysfunction document teach the element of administering an effective amount of at least one beta-blocker to result in a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject. Further, neither Rang nor the Autonomic Dysfunction document suggests this element. Rang is a review directed to finding non-invasive methods for measuring increased sympathetic activity in pregnant patients, with the goal of identifying those at risk for hypertension. The Autonomic Dysfunction document is a review of methods of assessing autonomic function. Therefore, neither reference discloses

producing a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject, as in the current claims.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker to produce a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject in at least a portion of the autonomic nervous system. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1 and 63 be withdrawn.

Claims 1, 16, and 18 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Guilli, et al. (Cardiovascular Research, 2001, 208-216) in view of Bugiardini, et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90) in view of Rang et al. (Rang, et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann, et al. (US 2004/0147969).

In making this rejection, the Office cites Guilli for allegedly teaching that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (abstract). However, Guilli does not teach the element of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering to the subject an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, as in the amended claims.

Guilli also does not suggest these elements, because Guilli is directed to evaluating the hypothesis that a parasympathetic dysfunction causes the autonomic imbalance in Syndrome X (abstract). There is therefore no suggestion of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Bugiardini also does not teach or suggest this element, because Bugiardini is directed to administration of verapamil, propranolol, and placebo to patients with Syndrome X. The treatment goal in Bugiardini is a heart rate under 60 beats per minute. There is therefore is no suggestion in Bugiardini of producing a parasympathetic activity/sympathetic activity ratio analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, as in the amended claims.

Therefore, the combination of Guilli and Bugiardini fail to teach or suggest all the elements of the rejected claims.

The Office also cites Rang for teaching non-invasive procedures for assessing autonomic cardiovascular control in patients with hypertensive disorder, and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. Mann was cited for teaching a control feedback loop, however a control feedback loop is not an element of these rejected claims.

However, as discussed above, neither Rang nor the Autonomic Dysfunction document teach or suggest the element of administering an effective amount of at least one beta-blocker to result in a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker to produce a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject in at least a portion of the autonomic nervous system. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 16, and 18 be withdrawn.

Claims 1 and 26-27 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hill, et al. (U.S. Patent 6,449,507) and Lampert, et al. (The Am J of Cardiology, 91, 2, Jan 2003) in view of Rang et al. (Rang, et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann, et al. (US 2004/0147969).

In making this rejection, the Office cites Hill for allegedly teaching the stimulation of parasympathetic and sympathetic nerve fibers and the administration of a drug such as propranolol for modifying the beating of the heart for a medical procedure. Hill does not teach modulation of the autonomic nervous system, however the Office alleges that Lampert teaches recovery of parasympathetic tone after acute myocardial infarction with the administration of propranolol. The Office alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention that administration of a beta blocker as in Lampert to stimulate the autonomic nervous system because of the teachings of Hill (Final Office Action, p. 18).

However, Hill does not teach the element of providing a subject known to suffer from an autonomic nervous system abnormality, or the element of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic

nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, as in the amended claims. Hill also does not suggest these elements, because Hill is directed to modifying the beating of the heart for a medical procedure (Abstract). There is therefore no suggestion of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

As discussed above, Lampert does not teach or suggest providing a subject known to suffer from an autonomic nervous system abnormality, or administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, and therefore Lampert does not make up for the deficiency in Hill.

The Office also cites Rang for teaching non-invasive procedures for assessing autonomic cardiovascular control in patients with hypertensive disorder, and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. Mann was cited for teaching a control feedback loop, however a control feedback loop is not an element of these rejected claims.

However, as discussed above, neither Rang nor the Autonomic Dysfunction document teach or suggest the element of administering an effective amount of at least one beta-blocker to result in a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of providing a

subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker to produce a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject in at least a portion of the autonomic nervous system. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, and 26-27 be withdrawn.

Claims 1, 11, 13, and 24 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Garrett, et al. (Quarterly J of Expt. Physiology, 1987, 72, 357-68) in view of Rang et al. (Rang, et al. J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann, et al. (US 2004/0147969.

In making this rejection, the Examiner states that Garrett teaches the administration of a beta-blocker such as propranolol to modulate the autonomic nervous system in salivary glands. However, Garrett does not teach the element of providing a subject known to suffer from an autonomic nervous system abnormality, or the element of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, as in the amended claims.

Garrett also does not suggest these elements, because the study was designed to evaluate factors which affect the secretion of kallikrein from the submandibular salivary glands in cats. There is absolutely no suggestion of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the

subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

The Office also cites Rang and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. Mann was cited for teaching a control feedback loop, however a control feedback loop is not an element of these rejected claims.

However, as discussed above, neither Rang nor the Autonomic Dysfunction document teach or suggest the element of administering an effective amount of at least one beta-blocker to result in a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of providing a subject known to suffer from an autonomic nervous system abnormality or of administering a beta-blocker to produce a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject in at least a portion of the autonomic nervous system. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 11, 13, and 24 be withdrawn.

Claims 1, 3, 4, 14, 19-22, 28, 41, and 62-68 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) in view of Rang et al. (J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann et al. (US 2004/0147969).

In making this rejection, the Office cites Gambardella for teaching the use of propranolol in elderly weight-losing cancer patients to block the effects of the

sympathetic nervous system. However, Gambardella does not teach the elements of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract). There is further no suggestion of these elements, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract).

The Office also cites Rang and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. However, as discussed above, neither Rang nor the Autonomic Dysfunction document teach or suggest the element of administering an effective amount of at least one beta-blocker to result in a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject.

The Office acknowledges that the references do not explicitly teach employing a control feedback loop, as in Claims 64-68. The Office therefore cites Mann for allegedly teaching therapeutic treatment for cardiac disease comprising sensors, and that patients can be titrated to appropriate beta-blocker dose levels based on the signals (Final Office Action, p. 25)

The Office concludes that it would have been obvious to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann, because "one having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the

patient's medical conditions" and further, "it would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensor in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol." (Final Office Action, p. 25-26)

However, the Applicants contend that as neither Rang nor the Autonomic Dysfunction document teach or suggest all the elements of the rejected claims, the addition of a control feedback loop allegedly taught by Mann fails to make up for this deficiency.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of providing a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker to produce a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject in at least a portion of the autonomic nervous system. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 3, 4, 14, 19-22, 28, 41, and 62-68 be withdrawn.

Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, and 62-68 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Brevetti et al. (Brief communications, Nov. 1981, parasympathetic 938-941) in view of Rang et al. (J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann et al. (US 2004/0147969).

In making this rejection, the Office cites Brevetti for teaching intravenous and oral administration of propranolol for treatment of Shy-Drager syndrome. However, Brevetti does not teach the element of administering a beta-blocker in an

amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human, as in the amended claims.

Brevetti also does not suggest this element, because the goal of treatment disclosed in Brevetti is treatment of primary orthostatic hypotension in Shy-Drager syndrome. There is therefore no suggestion of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human.

The Office also cites Rang and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. However, as discussed above, neither Rang nor the Autonomic Dysfunction document teach or suggest all the elements of the rejected claims, and therefore do not make up for the deficiency in Brevetti.

The Office further cites Mann for allegedly teaching a control feedback loop (Final Office Action, p. 28). However, as neither Rang nor the Autonomic Dysfunction document teach or suggest all the elements of the rejected claims, the addition of a control feedback loop allegedly taught by Mann fails to make up for this deficiency.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of administering a beta-blocker to produce a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject in at least a portion of the autonomic nervous system. Therefore, the combination of references does not render the current claims obvious.

Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, and 62-68 be withdrawn.

Claims 1, 21, 23-25, and 28 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Davies, et al. (The J of Intl Med Research, 1988, 16, 173-181) in view of Rang et al. (J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann et al. (US 2004/0147969).

In making this rejection, the Office cites Davies for teaching the administration of ibuprofen with an anti-hypertensive agent and a beta-blocker to patients with hypertension. However, Davies does not teach the element of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human, as in the amended claims.

Davies also does not suggest this element, because the goal of the study in Davies is to evaluate whether or not treatment of hypertension in patients on beta-blockers or thiazides is affected by the administration of ibuprofen. (Abstract). There is no discussion of the autonomic nervous system. There is therefore no suggestion of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human.

The Office also cites Rang and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. However, as discussed above, neither Rang nor the Autonomic Dysfunction document teach or suggest all the elements of the rejected claims, and therefore do not make up for the deficiency in Davies.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of administering a beta-blocker to produce a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject in at least a portion of the autonomic nervous system. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 21, 23-25, and 28 be withdrawn.

Claims 1 and 20 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Broder, et al. (U.S. Patent 6,284,800) in view of Rang et al. (J Hypertension, 2002) and Autonomic dysfunction document (Review, Oulu University, 2000) and further in view of Mann et al. (US 2004/0147969).

In making this rejection, the Office cites Broder for teaching bronchorestriction by administering an effective amount of D-propranolol (Final Office Action, p. 32). However, Broder does not teach the element of administering a beta-blocker in an amount effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human, as in the amended claims.

Furthermore, the Applicants point out that Broder discloses treatment with the isomer D-propranolol, not the more commonly used L-propranolol. As noted in the reference provided by the Office, "only L-propranolol is a powerful adrenoreceptor agonist, whereas D-propranolol is not". (p. 2-3 of Wikipedia reference on propranolol). Therefore, Broder does not teach the element of administering an effective amount of a beta-blocker, as the Office suggests.

Broder also does not suggest this element, because the stated purpose in Broder is to use "preferred" D-propranolol, which may "lack beta receptor blocking activites" with the associated side effects, which can cause problems for patients with asthma (col. 5, lines 36-42). There is therefore no suggestion of administering an effective amount of a beta-blocker, as in the current claims.

The Office also cites Rang and the Autonomic Dysfunction document (ADD) for teaching various methods to measure autonomic function. However, as discussed above, neither Rang nor the Autonomic Dysfunction document teach or suggest all the elements of the rejected claims, and therefore do not make up for the deficiency in Broder.

Therefore, a prima facie case of obviousness has not been established because Broder does not teach or suggest the element of administering an effective amount of a beta-blocker. The citation of Rang and the Autonomic Dysfunction document fail to make up for this deficiency. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1 and 20 be withdrawn.

New Claims 69-71 are patentable at least for the reasons discussed above.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number PALO-002.

Respectfully submitted,
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